جامعة بابل

كلية العلوم للبنات

قسم علوم الحياة

Application of nanoparticle technology to the treatment of rheumatoid arthritis

من اعداد الطالبات:

Duha haleem jasm

Shahlaa Khudair Abdulabbs

المرحلة : الرابعة

الدراسة :الصباحية

تحت إشراف الدكتور:

Dr.Sama Jawad Alzuwaini

السنة الجامعية 2022-2023م

بسم الله الرحمن الرحيم

(نَرْفَعُ دَرَجَاتٍ مَّن نَّشَاءُ ۗ وَفَوْقَ كُلِّ
ذِي عِلْمٍ عَلِيمٌ) سورۃ یوسف آیۃ ۷۶

صدق الله العلي العظيم

الاهداء

الى ابي الذي رسمني وامي التي لونتني ..

الى من قاسمني برحم امي ودم ابي ...اخوتي واخواتي

الى من اختبئت بظلهم من خيبات الامل

ومتاعب الحياة.. اصدقائي

الى من ضحوا من اجلنا

الى من تحملوا عناء الحرب لكي نعيش نحن

هؤلاء شهدائنا الابرار الذين اختاروا الشهاده لنعيش

نحن بعزة وكرامة لولا دمائهم الطاهرة الزكية لما

كنت الان اؤدي واجبي العلمي والذين ساهموا في

رفع راية الله اكبر في السماء رحمهم الله برحمته ....

بسم الله الرحمن الرحيم

(رجال صدقوا ما عاهدوا الله عليه فمنهم من

قضى نحبه و منهم من ينتظر وما بدلوا تبديلا)

صدق الله العلي العظيم

شكر وتقدير

بداية الشكر لله عزوجل الذي أعانني وشد من عزمي لإكمال هذا البحث

وبالشكر لمنقذ الأمة النبي محمد (صل الله عليه وآلة وسلم)...

أما بعد فلا يسعني أن أعبر عن ماتكن به نفسي وقلبي عن الشكر الجزيل لكل

من ساعدني لكي أصل لهذه المرحلة من حياتي العلمية وما هو إلا ثمرة تعب كل

ومن أستاذتنا ودكاترتنا أسأل الله أن يديم عليكم بالصحة والعافية ودوام التوفيق

لكي يتوفق من يأتي بعدي بجهودكم...

شكر خاص إلى صاحبة الفضل لإكمال هذا البحث ومساعدتي بأدق تفاصيله الدكتورة الفاضلة

Sama Jawad Alzuwaini

Application of nanoparticle technology to the treatment of rheumatoid arthritis

A B S T R A C T

Rheumatoid arthritis (RA) is one of the most common and severe autoimmune diseases related to joints. This chronic autoimmune inflammatory disease leads to functional limitation and reduced quality of life, since as there is bone and cartilage destruction, joint swelling, and pain. Current advances and new treatment approaches have considerably postponed disease progression and improved the quality of life for many patients. In spite of major advances in therapeutic options, restrictions on the routes of administration and the necessity for frequent and long-term dosing often result in systemic adverse effects and patient non-compliance. Unlike usual drugs, nanoparticle systems are planned to deliver therapeutic agents, especially inflamed synovium, to avoid systemic and unpleasant effects. The present review discusses some of the most successful drugs in RA therapy and their side effects and also focuses on key design parameters of RA-targeted nanotechnology-based strategies for improving RA therapies.

Keywords: Rheumatoid arthritis Nanoparticles Drug delivery Treatment

تطبيق تقنية الجسيمات النانوية في علاج التهاب المفاصل الروماتويدي

خلاصة

التهاب المفاصل الروماتويدي (RA) هو أحد أمراض المناعة الذاتية الأكثر شيوعًا وشدة المرتبطة بالمفاصل. يؤدي هذا المرض الالتهابي المناعي الذاتي المزمن إلى تقييد وظيفي وتقليل جودة الحياة ، حيث يسبب الم شديد و تدمير للعظام والغضاريف وتورم المفاصل. أدت التطورات الحالية وأساليب العلاج الجديدة إلى تاخر تطور المرض إلى حد كبير وتحسين نوعية الحياة للعديد من المرضى. على الرغم من التقدم الكبير في الخيارات العلاجية ، فإن القيود المفروضة على طرق الإعطاء وضرورة الجرعات المتكررة وطويلة الأجل غالبًا ما تؤدي إلى آثار سلبية جهازية وعدم امتثال المريض. على عكس الأدوية المعتادة ، تم التخطيط لأنظمة الجسيمات النانوية لتوصيل عوامل علاجية ، وخاصة التهاب الغشاء الزلالي ، لتجنب الآثار الجهازية وغير السارة. تناقش المراجعة الحالية بعضًا من أنجح الأدوية في علاج التهاب المفاصل الروماتويدي وآثارها الجانبية وتركز أيضًا على معايير التصميم الرئيسية للاستراتيجيات القائمة على تقنية النانو المستهدفة لالتهاب المفاصل الروماتويدي (RA) لتحسين العلاجات.

Contents

1. Introduction

Rheumatoid arthritis is an autoimmune disease and chronic systemic inflammatory disorder which is characterized by chronic synovitis that often leads to tissue dysfunction such as localized damage to articular cartilage, bone, tendon and ligament, followed by loss of function [1,2]. While the etiology of RA is unclear [3], various immune components including the innate immune system, various cells (such as B cells, T cells, macrophages/ synoviocytes) and humoral factors, such as cytokines (TNF-a, IL- 1b,IL-6 and IL-17A), chemokines, cell adhesion molecules, and matrix metalloproteinases, as well as genetic susceptibility to environmental factors have been postulated to play a critical role in the pathogenesis of RA [4]. The prevalence of RA has been estimated to be around 40/100,000 (greater than 0.5–1%) of the population worldwide, being women 2:1 to 3:1 to be affected more than men. Generally the lifetime risk of RA in adults is 3.6 percent (1 in 28) for women and 1.7 percent (1 in 59) for men [3,5,6]. Advances in the RA therapeutics were associated with the downregulation of disease progress and inhibition of joint damage, however, these need a frequent and long-term administration of drugs which result in unwanted systemic side effects [1]. Nanotechnology is a promising multidisciplinary method that use a various array of tools and techniques in order to the diagnosis or treatment of diseases with the use of nano-sized materials. By using these nano-sized carriers, we can selectively deliver therapeutic agents to the desired site of inflammation in a controlled or sustained manner [1,7]. This review focuses on the emerging concepts regarding the therapeutic potential of nano-technology in the RA.

2. Rheumatoid arthritis

2.1. Pathogenesis

The inflammation of RA originates in the synovium; the synovial tissue shows synovial lining hyperplasia as a result of fibroblast-like synoviocytes (FLS) and macrophage-like synovio-cytes (MLS) accumulation. These macrophages and fibroblast-like cells promote inflammation by producing chemical mediators such as pro-inflammatory cytokines such as TNF-a and IL-1b [8]. Furthermore, both of them induce synovial cells to release tissue

degrading matrix metalloproteases (MMPs) and TNF-a stimulates the development of osteoclasts, which are responsible for bone abrasion. Consequently, more macrophages, lymphocytes, and fibroblasts are activated and the RA inflammatory process remains [7,8]. Studies have also showed that TNF-a and IL-17 have synergistic effects in promoting the activation and expression of IL-1, IL-6, and IL-8, granulocyte colony-stimulating factor (G-CSF) and MMPs, all of which play a major role in progress of inflammation and cartilage degradation [9,10]. These inflammatory cytokines are abundant in the synovial fluid and synovium of RA patients which have a potent capacity to induce receptor activator of nuclear factor_ b ligand (RANKL), which is the main regulator of osteoclastogenesis, on synovial fibroblasts and bone derived stromal cells and affect osteoclast signaling, therefore directly causing bone destruction process (Fig. 1) [11]. Angiogenesis is of the initial hallmarks in the inflamed RA synovium. Upregulation of pro-angiogenic and downregulation of anti-angiogenic factors in RA enhance the proliferation of endothelial cells and angiogenesis process [12–14]. Several proangiogenic factors such as growth factors (VEGF,TGF, FGF, EGF, PDGF), cytokines (TNF-a, IL-1b, IL-6, IL-17, IL-18), chemokines (CXCL8, CXCL12, CCL2, CXC3L1), pro-teases (metalloproteases (MMPs)), adhesion molecules (avb3 and avb5 integrins, VCAM-1, ICAM-1) are involved in the angiogenesis during RA [7]. It has recently demonstrated that Notch receptors (Notch 1–4) and their ligands (Jagged 1–2, Delta 1,3,4) are over- expressed in the synovial tissue of patients with RA and enhance inflammation and angiogenesis [15–17]. Thus inhibition of angiogenesis may stop the inflammation and represent a new approach to the treatment of RA.

2.2. Genetic aspects of rheumatoid arthritis

The genes encoding several proteins such as human leukocyte antigens which encodes the polymorphic b-chain of the DR molecule (HLA-DRb1), protein tyrosine phosphatase non receptor 22 (PTPN22), Cytotoxic T lymphocyte antigen 4 (CTLA4), tumor necrosis factor-a-induced protein 3 (TNFAIP3), C-C chemokine receptor type 6 (CCR6) and signal transducer and activator of transcription 4 (STAT4) can be considered as risk factor for RA [2,18].

2.3. Environmental factors and rheumatoid arthritis

In addition to genetic factors, environmental factors such as bacterial and viral infections can also be associated with polyarthritis in patients who are genetically susceptible. It is suggested that bacterial and viral infections through mechanisms such as molecular mimicry, epitope spreading, and the expression of superantigens can induce RA [19]. Accordingly, it is demon-strated that porphyromonas gingivalis may induce citrullination of proteins, which then lead to activation of both citrulline-specific pathogenic Tcells and anti-citrullinated protein antibodies (ACPAs) producing B cells. Subsequently, ACPAs react with citrullinated joint proteins, which leads to induction of local inflammation leading to chronic RA [19]. Smoking, alcohol intake, birthweight, breastfeeding, socioeconomic status and ethnicity are other environmental risk factors for RA [20].

2.4. Serological features

Rheumatoid factor (RF) and ACPA are two most important markers used to diagnosis of RA. Antinuclear antibodies (ANA) and anti-double-stranded (anti-ds) DNA antibodies may also be present in patient with RA [3,21,22]. By using acute phasereactants such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), we can measure the disease activity [23,24].

2.5. Collagen-induced arthritis (CIA) in mice as a model for RA

CIA in DBA/1 mice is the most used animal models for RA [25]. Immunization of rats with an emulsion of collagen type II (CII) in complete Freund’s adjuvant (CFA) leads to polyarthritis in association with production of CII-specific antibodies and RF [25].

3. Therapeutic approaches

Current therapeutic regimen for RA patients includes nonste-roidal anti-inflammatory drugs (NSAIDs), glucocorticoids, disease-modifying anti-rheumatic drugs (DMARDs) and Biological drugs [1,7]. While treatment has progressive from NSAIDs to DMARDs, and modern biologics, these drugs in use have potentially life threatening consequences,

because of non-specific targeting, and every so often along with impaired immune function [26].

3.1. Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs such as indomethacin [1-(4-chlorobenzoyl)-5- methoxy-2-methyl IMCol-3-yl] acetic acid, aspirin, ibuprofen, naproxen, and Celecoxib decrease pain (Analgesia) in the early stage of RA through anti-inflammatory mechanisms without loss of articular function. NSAIDs block cyclooxygenases; COX-1 and COX-2, enzymes which play a key role in inducing pain and inflammation by generate prostaglandins (PGs). Due to their limited effectiveness, inability to modify disease course in the long term, and various side effects include gastrointestinal disturbance and renal malfunction and cardiovascular risk, their prescription is associated with several problems [1,7,27].

3.2. Glucocorticoids

Glucocorticoids such as prednisolone and dexamethasone are considered as anti-inflammatory agents that inhibit a phospholip-id release which leads to downregulation of joint inflammation. These drugs can be used in patients with RA during the first 2 years of treatment. As the long-term use of glucocorticoids (GCs) causes several side effects such as impaired glucose metabolism (insulin resistance), cardiovascular diseases, skin thinning, osteoporosis, hypertension, obesity and inhibition of wound repair, their systemic applications are limitid. However, approximately 44% to 75% of patients use glucocorticoids. Numerous studies have recommended that low-dose GCs may have disease modifying effects in RA [1,28].

3.3. Disease-modifying antirheumatic drugs (DMARDs)

DMARDs were first used in the late 1980s that have specific antirheumatic activities. Since clinical outcomes of DMARD appear 1–6 months after the first use, they have also been entitled as ‘slowly acting antirheumatic drugs [29]. DMARDs such as methotrexate alter the course of RA progression and decrease joint destruction. Methotrexate in combinations with NSAIDs or GCs or other conventional DMARDs can exert effective function [30]. There are other DMARDs such as sulfasalazine, hydroxy- chloroquine,

leflunomide and gold salts, which are usually used as substitute to or in combination with methotrexate. The side effectsof DMADRs are including hepatic cirrhosis, interstitial pneumoni-tis, myelosuppression, hypersensitivity and allergic reactions, and retinopathy [29].

3.4. Biological drugs

Biological drugs are complex proteins produced in prokaryotic or eukaryotic cells by molecular biology methods [31]. This class includes cytokine antagonists (TNF blockade by **infliximab**, **etanercept**, **adalimumab**, **golimumab**; IL-1 receptor blockade by **anakinra**; and IL-6 receptor inhibitor by **tocilizumab**), B-cell depleting agents (**rituximab**), and T-cell costimulation modulator (**abatacept**) and kinase inhibitors (like the p38 MAPK inhibitors, Syk inhibitors, Jak inhibitors (**tofacitinib**), IkB inhibitors) [1,7,30,32]. The biological drugs, especially TNF inhibitors in combination with methotrexate, exhibit high efficacy in patients when therapy is begun early in the course of the disease. Despite these remarkable statistics, numerous problems are associated with current biological therapy, such as high costs, risk of serious bacterial infections and failure to keep up response over time [33]. Treatment options for RA are summarized in Table 1.

3.5. Gene therapy

Gene therapy is another approach by which nucleic acids deliver into the cell to suppress expression of disease promoting proteins. In RA, gene therapy is local and joint-specific targeted approach to both silence expression of proinflammatory cytokines genes (TNF-a, IL-1b, and IL-6) or high-expression anti-inflamma-tory cytokines genes (IL-1ra, IL-4, IL-10, IFN-b), so is hopefulness for that long-term expression of these anti-arthritic agents will result in persistent anti-inflammatory effects whereas preventing systemic adversative reactions [7]. Viral vectors, including retroviral (RV), adenoviral (AdV), and adeno-associated virus (AAV) vectors has been explored for gene therapy in RA both in animal models and a few clinical trials [34]. However, nonviral, nanotechnology-based vectors for gene therapy show many advantages to viral-based vectors, such as low immunogenicity, no insertional mutagenesis, and no risk of infection [7,35,36].

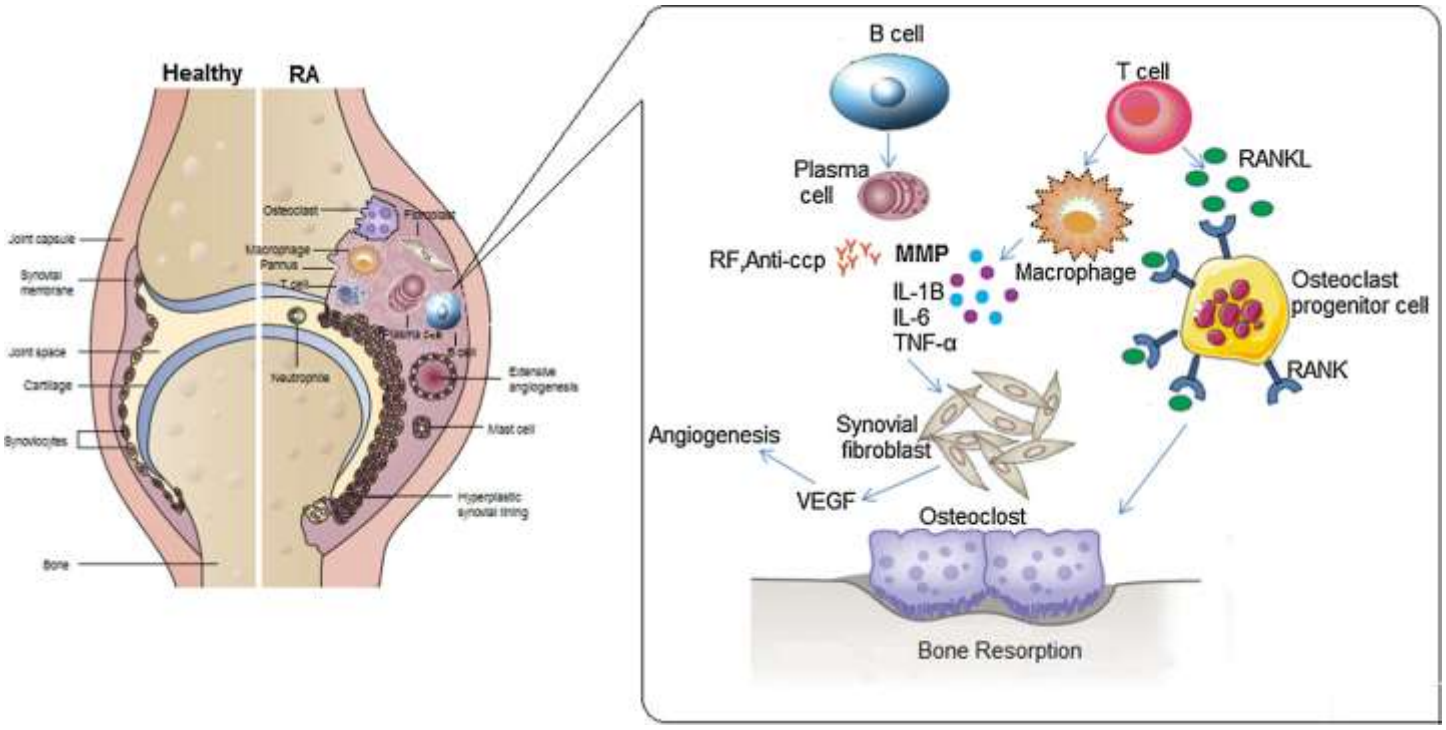

Fig. 1. Pathogenesis of rheumatoid arteritis. Rheumatoid arthritis is an autoimmune disease and chronic systemic inflammatory disorder. Rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs) are two most important autoantibodies usually produced by plasma cells. T cells activation leads to overproduction of inflammatory cytokines, including TNF-a, IL-1b, and IL-6 by macrophages. These inflammatory cytokines have a potent capacity to induce receptor activator of nuclear factor_ b ligand (RANKL), which is the main regulator of osteoclastogenesis. Also production of vascular endothelial growth factor (VEGF) by synovial fibroblasts stimulates angiogenesis, which maintains the inflammation by recruiting more inflammatory leukocytes. All of these components play a major role in progress of inflammation and cartilage degradation and bone destruction process.

Table 1
Current treatment options for rheumatoid arthritis.

Drugs	Mechanism of action
NSAIDs	Inhibition of COXs
	Reduce acute inflammation thereby decreasing pain(Analgesia)
GCs	Prevention of phospholipid release
	Anti-inflammation
	Immunosuppression
DMARDs	Immunosuppression
	Disease-altering activity
Biologic drugs	Antagonism of cytokine actions
Anti-cytokines	
Anti-T cell	T-cell costimulation modulator
Anti-B cell	B-cell depleting agents
Kinase inhibitors	Antagonism of cytokine actions

4. Drug carriers for treatment of RA

4.1. Nanoparticles

Nanotechnology and Nanoparticles (NPs) have a wide range of applications in biology. Nanotechnology enable the making of devices on the same scale as individual cells and biomolecules, creating an unique approach to imaging, sensing, drug delivery and characterizing basic biological processes(Fig. 2). Nanoparticles have at least one dimension in the scale of 0.1–100 nm [37]. Liposomes, micelles, metallic nanoparticles, and polymeric nano-particles are of the most commonly used nanoparticulate carrier systems for drug delivery [26]. Various nanoparticles exhibit a wide variety of physical and chemical properties such as size, surface area to mass ratio, and surface charge that can significantly affect their biomedical potential [37]. Nanoparticles are able to: (a) encapsulate and save drugs from degradation, (b) improve targeted drug delivery (c) control drug release, and (d) be produced in large, reproducible, scale [38]. NPs can be targeted by active targeting and passive targeting under in vivo conditions. Properties that mediate passive targeting process include particle structure, size, shape, and surface characteristics. Targeting of macrophages using a nanocarriers system was an approach that was studied primary on as it was known that the presence of macrophages is increased in inflamed joints and nanoparticles can be efficiently phagocy- tosed by macrophages even without surface modifications. This approach is known as passive targeting [7]. Targeting of macro-phages through systemic administration of nanocarriers systems has also been actively followed. These approaches take advantage of the fact that macrophages are central players in RA and nanocarriers can be taken up by macrophages into arthritic joints through inflamed leaky capillaries, an effect known as enhanced permeability and retention (EPR) [7]. However, systemically administered nanocarriers can also be cleared quickly by macro-phages exist in the reticulo-endothelial system (RES), so declining the availability of drugs reaching the inflamed joints. Thus, surface modifications of nanocarriers to delay RES interaction and active targeting of other organ systems or immune cells and pathways are constantly being explored. Active targeting involves the use of targeting ligands for enhanced delivery of NP systems to a specific site. Typical targeting ligands include small molecules, peptides, antibodies and their

fragments, and nucleic acids [7,39]. Nano-particles can be taken by blood cells through various mechanisms such as adsorption, ligand-receptor attachment, covalent coupling, and internalization [38]. For example, macrophages have been used to deliver internalized antioxidant enzyme catalase nano-particles, named nanozymes, across the blood–brain barrier (BBB). Delivery of nanozymes via macrophages was also tracked and showed increased nanozyme, and likely catalase, persistence in the brain of Parkinson's disease model using MPTP intoxicated mice as compared to nanozymes alone [40]. Nanozymes delivered via macrophages were able to inhibit neuroinflammation, reduce astrocytosis, reduce oxidative stress, increase neuron survival and induce a neuroprotective effect that prevents inflammation in the brains of MPTP-intoxicated mice [38].

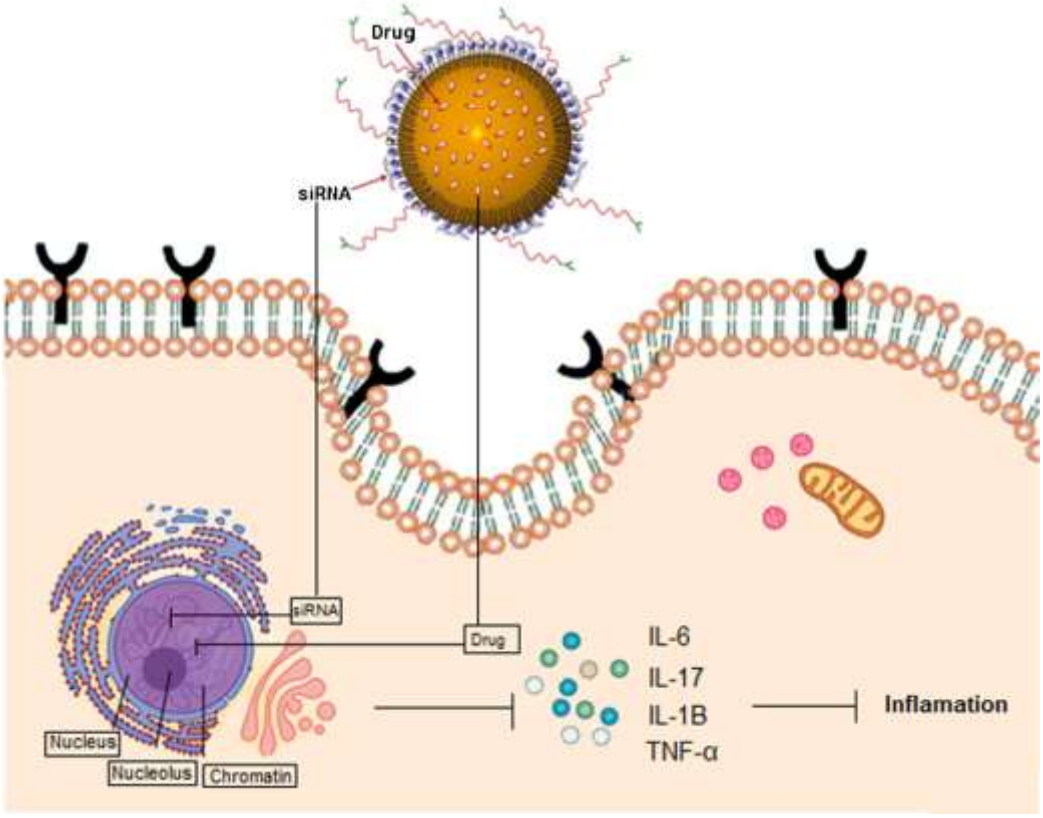

Fig. 2. Nanoparticle (NP) approach in rheumatoid arthritis. Different types of nanoparticles have been used for treatment RA. Drugs and siRNA against cytokines transported by these NPs prevent expression of pro-inflammatory cytokines and inhibits the activation of inflammatory and cartilage degeneration.

5. Nanoparticles for treatment of rheumatoid arthritis

There are different examples of nanomedicine-based approaches for simultaneous targeted therapy, based on lipo-somes, polymeric NPs, chitosan NPs, iron oxide nanoparticles, gold nanoparticles, albumin-bound and antibody-conjugated nano-particles.

5.1. Liposomes

The first NP platform was the liposomes. Liposomes are spherical vesicles that have a single or multiple bilayered structure of lipids that self-assemble in aqueous systems [41]. Liposomes exhibit various features such as diverse range of constructions, capabilities to carry and protect many types of biomolecules, and biocompatibility and biodegradability [41]. These advantages have led to the well-characterized and wide use of liposomes as transfection agents of genetic material into cells (Lipofection) in biology research [39]. Lipofection generally uses a cationic lipid to arrangement a collective with the anionic genetic material. Another major application of liposomes is their use as therapeutic carriers since their design can allow for setup of hydrophilic compounds within the core and hydrophobic drugs in the lipid bilayer itself. For lipophilic drugs such as indomethacin, lipid nanospheres with internal oil phase enclosed by a phospholipid monolayer show better loading capacity [7]. Encapsulation developments the anti-inflammatory activity of indomethacin, even though reduces the gastrointestinal side effects [7]. The integration of polyethylene glycol (PEG) to lipid microspheres (LM) postpones their uptake by the reticulo-endothelial system (RES) and increases their circulation time and bioavailability and leads to higher accumulation of the encapsulated nonsteroidal anti-inflammatory drugs (NSAID) in paws of arthritic rats [42,43]. Nanoencapsulation of NSAIDs exhibited potent anti-inflammatory effects, as evidenced by decreased serum levels of pro-inflamma-tory cytokines such as TNF-a and IL-6 and enhanced levels of the anti-inflammatory cytokine like IL-10 [7,44]. Prednisolone loaded small PEG-liposomes (_100 nm) persisted in the circulation with a half-life of 50 h and a single systemic administration of this nanoformulation led to complete remission of inflammation within 2 days, with the effect durable for 2 weeks [45]. It has also been

demonstrated that a single administration of campto- thecin (CPT) loaded micelles to arthritic joints in a CIA model was associated with ameliorating effects [46]. Additionally, combina-tion of vasoactive intestinal peptide (VIP) and CPT and sterically stabilized micelles (SSM) further decreased the therapeutic dose of CPT by 10-fold and effectively declined joint inflammation in CIA mice for at least 32 days without detectable systemic toxicities [7]. SiRNA complexion with cationic liposomes (lipoplexes) directed against TNF-a, IL-1, IL-6, or IL-18 could also significantly reduce the severity of arthritis [47]. The most important disadvantage of lipoplexes is the short-lived interval of silencing about 1 week, so needing repeating injections to maintain therapeutic effect [7].

5.2. Polymeric nanoparticles

Polymeric NPs formed from biocompatible and biodegradable polymers have been broadly studied as therapeutic carriers. Polymeric NPs are formulated through block-copolymers of different hydrophobicity. These copolymers spontaneously gather into a core-shell micelle formation in an aqueous environment [48,49]. Polymeric NPs can encapsulate hydrophilic and/or hydrophobic small drug molecules, additionally proteins and nucleic acid macromolecules [39]. Dendrimers are polymeric NPs with branched structure made from synthetic or natural elements including amino acids, sugars, and nucleotides [50]. In contrast to liposomes, polymeric NP-loaded drugs are released slowly and require less frequent administration. Combined NPs of poly (D,L-lactic/glycolic) (PLGA)/poly(D,L-lactic acid) (PLA) homopolymers and PEG-PLGA/PLA form copolymers encapsulating b-methasone to observe the therapeutic activity of GCs in adjuvant-induced arthritis (AA) rats and antibody-induced arthritis in mice [7]. The polymeric nanoparticles gathered at the target sites through enhanced EPR effect and following the loss of PEG, were phagocytosed by resident inflammatory macrophages, letting continual release of GCs during the period of 14 days [7,51,52]. The branching structure of dendrimers can trap small drug molecules and also increasing the solubility of hydrophobic drugs such as NSAIDs by covalently attached the functional groups at end of dendrimers to these drugs [7]. A cyclodextrin polymer (CDP) conjugated a-methylprednisolone (MP) self-assembled into NPs with a size of 27 nm could inhibit

the proliferation of human lymphocytes and reduce the symptoms of CIA in mice [53]. In another study, the oral administration of indomethacin (IMC) nanoparticles into the adjuvant-induced arthritis (AA) rats was associated with amelioration effects [54]. Nagai and his colleague have also demonstrated the preventive effects of topical use of IMC solid NPs in AA rats. The results showed that the dermal application offers many advantages over conventional oral delivery such as decreased the maximum plasma concentration of the drug and increased tolerability profile and achieve of high local drug concentration without systemic lateral effects [55]. Activated but not resting macrophages express folate receptor b (FRb), which can be exploited to deliver folate-targeted nanoparticles, as specific drug delivery systems to RA therapy. In this way, folate-targeted therapies selectively attack the pathologic cell type, leaving the healthy macrophages unharmed. Furthermore, since no other population of white cells appears to express a functional FRb, the level of toxicity associated with folate-targeted therapy appears to be very low [56]. The activity of an folic acid (FA) and methotrexate (MTX)—conjugated poly (amidoamine) dendrimer (generation 5) (G5-FA-MTX) as a therapeutic for the inflammatory disease of arthritis investigated [57]. Administration of folic acid (FA) and methotrexate (MTX)— conjugated poly (amidoamine) dendrimer (generation 5) (G5-FA- MTX) into CIA rats led to selective killing of macrophages through FRb and suppression of inflammation and arthritis [57]. Curcumin and actarit was described for application in treatment of RA. Curcumin has beneficial anti-oxidant, anti-cancer, and anti-inflammatory effects, with low side-effects [58]. Several strategies were developed to enhance oral bioavailability of curcumin such as encapsulation by polymeric compound like carboxy methyl cellulose acetate butyrate (CMCAB) by flash nano precipitation method using Multi Inlet Vortex Mixer (MIVM) [59]. SLNs are a new approach to deliver curcumin into the inflamed joints and progress its biopharmaceutical performance. Curcumin loaded solid lipid nanoparticles (C-SLNs) ameliorate complete Freund's adjuvant (CFA)-induced arthritis in rats through reduc-tion of oxide-inflammatory and immunodulatory cascade [60]. Actarit is an orally active DMARDs and a poor water soluble anti-rheumatic drug. The intravenous administration of actarit loaded solid lipid nanoparticles (SLNs) may improve therapeutic efficacy and reduce side-effects commonly associated with oral formulations of actarit [61]. Accordingly, it is

demonstrated that actarit-loaded SLNs may serve as passive targeting agents in RA and may provide lengthy residence time of the drug and reducing dosing frequency and low toxicity, in that way improving patient compliance [61]. The intravenous administration of MTX-PLGA-Au NPs into the CIA mice was associated with accumulation of nanoformulations in the inflamed region. Moreover, arginine-glycineaspartic acid (RGD) targeted NPs in combination with near-infrared (NIR) irradiation exhibited greater therapeutic efficacy with a much smaller dosage of MTX [62]. The RGD-MTX-PLGA-Au nanoparticle-based treat- ment combined with NIR irradiation had greater therapeutic efficacy with a much smaller dosage of MTX in the nanoparticles. These results suggest that the targeted chemo-photothermal treatment via multifunctional NPs is an effective strategy for maximizing the therapeutic efficiency and minimizing dosage- related side effects in the treatment of RA [62]. PLGA NPs targeted with RGD peptides have been used for STAT1 siRNA delivery, so because of presence the RGD peptide on the NPs increased paw tissue uptake in arthritic mice. STAT1 was silenced leading to an increase in expression of IL-10 mRNA [10,63]. Moreover, PLGA-collagen type II (CII) NPs significantly inhibited CIA and TNF-a expression in treated animals, and decreased the sustained release of collagen from PLGA that imply a suitable delivery system for oral tolerance induction [64,65]. Hyaluronan is a natural polysaccharide in the extracellular matrix of the body and binds to the CD44 receptor, which is over-expressed by synovial lymphocytes, macrophages, and fibroblasts at the inflamed joint of RA patients [66]. Blockade of Notch signaling with g-secretase inhibitors ameliorates the progression of RA in a collagen-induced arthritis (CIA) model [67]. A g-secretase inhibitor (DAPT) loaded hyaluronan NPs (HA-NPs) were prepared as potential therapeutics for RA. In vivo biodistribution of the DAPT-loaded HA-NPs (DNPs) was investi- gated using non-invasive near-infrared fluorescence (NIRF) imag-ing system after systemic administration to a CIA mouse model. DNPs could significantly reduce the production of pro-inflamma-tory cytokines (TNF-a, IFN-g, MCP-1, and IL-6, IL _12, IL _17) and collagen-specific auto-antibodies (IgG1 and IgG2a) in the serum of the CIA mice [68]. Antagonism of avb3 integrin decreased synovial angiogenesis and clinical disease in animal models. avb3 targeted perfluorocarbon (PFC) or perfluorooctylbromide (PFOB) nano-particles administered systemically localized to the inflamed joints and suppressed

inflammatory arthritis when conjugated to the antiangiogenic drug fumagillin. Fumagillin is a mycotoxin made by Aspergillus fumagatus that inhibits the metalloprotease methionine aminopeptidase-2, an enzyme involved in neovascularization. MetAP-2 inhibition by fumagillin perturbed angiogenesis, by modulation of the noncanonical Wnt pathway signaling and erk1/2 phosphorylation, level is severely controlled during angiogenesis [14,69,70]. The use of avb3 mainly as a targeting receptor for the delivery of anti angiogenic drugs to suppress the progression of arthritis and decrease in the number of inflamma-tory cells recruited into the subsynovial space. A single systemic dose of fumagillin-PFC NPs synergized with MTX provide significant anti-inflammatory effects with a favorable safety profile in a mouse model of arthritis [71].

5.3. Chitosan

Naturally occurring polymers, principally of the polysaccharide type, have been used pharmaceutically for the delivery of a wide variety of therapeutic agents. Chitosan, the second abundant naturally occurring polysaccharide next to cellulose, is a biocom-patible and biodegradable mucoadhesive polymer that has been broadly used in the preparation of micro as well as nanoparticles [72]. Chitosan is a non-toxic biodegradable polycationic polymer with low immunogenicity. Chitosan, a natural copolymer of N-acetylglucosamine and D-glucosamine, is attractive for encapsu-lating quantum dots (QDs) because it enables properties such as chelation of metal ions, water solubility and ease of processing [73]. Chitosan and dextran are two promising biodegradable polymers for targeted drug and gene delivery via conjugation with folic acid, galactose and transferrin [73,74]. Chitosan nanother- apeutics have received great attention in the field of oncology because of enhanced tumor targeting, ability to load different hydrophobic anticancer drugs, and the ability to control the anticancer drug release rate [75]. The siRNA-NPs were effectively produced by encapsulating polymerized siRNA (poly-siRNA) into thiolated glycol chitosan (tGC) nanoparticles in aqueous condition. Inhibition of Notch1 with siRNA-NPs caused to retarded progres- sion of inflammation, bone erosion, and cartilage damage in CIA mice. Novel Notch1 targeting siRNA delivery system of siRNA-NPs showed effective RA treatment by suppressing Notch1 signaling pathway without unwanted severe toxicity. Thus, Notch1 inhibiting siRNA-NPs

demonstrated the great potential in RA therapeutics that was hard to be achieved using conventional drugs [76]. In another study, a nanocomplex of polymerized siRNA against TNF-a with thiolated glycol chitosan (tGC) improved the accumulation of poly-siRNA in arthritic joints, when internalized in activated macrophages and suppressed the expression of target mRNA in a sequence-specific manner [77]. Other examples of gene therapy in animal models of arthritis include the over-expression of IL-1 receptor antagonist (IL-1ra, a naturally occurring anti-inflammatory molecule) by chitosan DNA NP and systemic delivery of siRNA lipoplexes that silence cytosolic phospholipase A2a (cPLA2a, a key molecule involved in inflammation and pro- inflammatory cytokine production) [78,79]. Chitosan coated calcium phosphate encapsulating iron saturat-ed bovine lactoferrin nanocarriers (C-CP-Fe-bLf —NCs) have been used for delivery of Fe-bLf in CIA mice. Oral administration of these NCs in mice was found to be non-toxic and has the ability to reduce joint inflammation and significantly inhibit the expression of IL-1b, nitric oxide, c-Jun N-terminal kinase (JNK), and MAPK [10,80]. The C-CP-Fe-bLf —NCs showed the ability to completely dissolve the calcium pyrophosphate crystals in mice joints, and prevents their accumulation in the joints, therefore, prevents expression of pro-inflammatory cytokines TNF-a and IL-6, degradation of cartilage, and progression of RA [80].

5.4. Iron oxide

Iron oxide NPs are good-looking nanosystem because of their strange physical properties, biocompatibility, inexpensiveness, and their ability to target specific locations, minimizing damage to peripheral organs [28]. These magnetic NPs can be co-encapsulat-ed along with drug molecules into NPs of other material such as poly (lactic-co-glycolic acid) (PLGA). Being a well-defined, biodegradable and biocompatible polymer, PLGA has attracted great attention: iron oxides NPs, when co-encapsulated into drug-loaded PLGA NPs, become protected from degradation and the drug release can be persistent and controlled. Also, there is the possibility to modify these NPs surface properties to arrange for stealth and selectivity to specific cells, organs or tissues. Furthermore, iron oxide NPs can be used as imaging contrast agents, illustrating the application of nanotechnology to medical monitoring and diagnosis [81]. Iron oxide NPs are a passive

and active targeting imaging agent which are mostly superparamag-netic [39]. Superparamagnetic iron oxide NP (SPION) is composed of iron oxide as core with a hydrophilic coat of dextran or another biocompatible compound to upturn their steadiness [82]. SPIONs commonly used as a magnetite (Fe3O4) and/or maghemite (gFe2O3) core [39]. SPIONs have some benefits such as decreased toxicity and increased imaging sensitivity and specificity [83]. SPION agents, ferumoxides (120–180 nm) and ferucarbotran (60 nm) are clinically used for MRI. SPIONs have also been approved in molecular imaging applications like the recognition of apoptosis and gene expression. Progresses in tissue engineering have emphasized the role of mesenchymal stem cells (MSCs) in treating RA [84–86]. Their specific self-renewal, multipotent differentiation ability (osteoblasts, chondrocytes and adipocytes), immunosuppresssive and anti-inflammatory properties are all key characteristics linked to their success in stem cell-based therapies [85,87]. The immunosuppressive properties of MSCs are of particular interest in treating RA. MSCs derived cytokines for example IL-10, IL-6, IL-11 and TGF-b inhibit T cells and dendritic cells function and release of soluble antigens such as HLA-G, efficiently deactivates NK cells and moderate dendritic cell and T cell action. Furthermore, secreted immunosuppressive enzymes, such as indoleamine 2,3-dioxygenase (IDO), suppress leukocytes [85,86,88]. SPIONs can be used in combining with the employ of magnetic resonance imaging (MRI) to image and track MSCs in vivo within a murine model of RA [89]. Stem cells are fortified to internalize SPIONs; by this method, the magnetic cargo can be transported into the cells. The intracellular iron disrupts the local magnetic field so let cells to be visualized as a lack of signal with MRI [89–92]. MSCs have been used to regenerate and repair the function of damaged tissue, such as cartilage. The remarkable ability of MSCs is migration toward the site of injury, with surrounding tissues and differentiates into cartilage though suppressing the immune system that highlighted their applicabil-ity as a possible therapy for RA. These studies were demonstrating the potential of MSCs in treating RA [85,86,89,93]. In one study polyethyleneimine (PEI)-SPION have also been used for the systemic delivery of IL-2/IL-15Rb-siRNA to arthritic rats. PEI-SPION-delivered siRNA displayed negligible cytotoxicity, improved siRNA stability, accumulated easily in inflamed joints and was efficiently taken up by joint macrophages and T cells [94].

5.5. Gold NPs

Gold NPs have useful properties such as biocompatibility and superficial modification. This NPs can strongly enhance optical processes such as light absorption, scattering fluorescence, and surface-enhanced Raman scattering (SERS) because of the unique interaction of the free electrons in the NP with light, so can use in many applications such as biochemical sensing and recognition, biological imaging, diagnostics and healing applications [39,95]. Gold NP probes have also been used to detect heart disease and cancer biomarkers. They can also transform absorbed light into heart and consequently, is probable for infrared phototherapy [96–98]. Nanogold particles such as gold salts (sodium gold thiomalate) which have anti-angiogenic properties, were usually used in the treatment of RA earlier than the development of biologics drugs [7]. Nanogold may be useful when conjugated with other biologics or DMARDs. Long-standing gathering of gold salts often causes serious nephrotoxici- ty [99]. Anti-arthritic activities of gold nanoparticles (Au NPs) have been investigated in an effort to avoid side effects. In one study, rats that had been chemically induced to exhibit symptoms of inflammation were treated with either Au NPs or sodium aurothiomalate [100].Those treated with Au NPs showed a greater reduction in the severity of symptoms, encouraging further investigations. Moreover, studies focusing on cell systems provid- ed clues as to how Au NPs may elicit their anti-inflammatory activity. For example, they inhibit production of reactive nitrogen and oxygen species, as well as activation of NF-kB [101]. In addition, Au NPs do not induce secretion of the proinflammatory cytokines TNF-a and IL-1b [101,102]. In one study, tocilizumab- loaded hyaluronate-gold nanoparticles (HA-AuNP/TCZ) targeted with a monoclonal antibody against IL-6 has also been tested in CIA mice. AuNP was used as a drug carrier with antiangiogenic effect [103]. These results support the need to further explore the potential of Au NPs as anti-RA agents.

5.6. Albumin-bound

Albumin is a beneficial attractive biomaterial or carrier for many therapeutics in treating a variety of diseases including cancer, arthritis and diabetes [104]. Albumin naturally binds to the hydrophobic molecules with non-covalent mutable binding, avoiding

solvent-based toxicities for therapeutics [105]. Interest- ingly, albumin has special ability for arthritis targeting because it markedly collects in inflamed tissues in arthritis. Albumin-bound NPs use the endogenous albumin paths to transport hydrophobic molecules in the bloodstream [106]. Albumin has been studied as a protein carrier for drug delivery. It is biodegradable, nontoxic, non-immunogenic, stable over a wide pH range (4–9), and could be heated at 60 _C for up to 10 h [107]. Methotrexate conjugate with human serum albumin (MTX-HSA) considerably decreased syno-vial fibroblast invasion and cartilage degradation in a humanized RA model using severe combined immunodeficient mice [108]. Tacrolimus (FK 506; TAC) is a highly lipophilic 23-member macrolide lactone antibiotic isolated from Streptomyces tsuku-baensis that is primarily used clinically as an immunosuppressant [109]. TAC has noticeable anti-arthritic activity in rodents through the overwhelming of inflammation and expression of TNF-a and IL-1b, which reduces damage to bone and cartilage. TAC is therapeutically effective in RA patients following the failure methotrexate treatment. TAC-loaded human serum albumin (HSA) nanoparticles (TAC HSA-NPs) displayed significantly more anti-arthritis activity than TAC formulations including intrave- nously administered TAC solution or oral TAC suspension [110]. TAC HSA-NPs are a hopeful drug delivery system to enhance water solubility and increase accumulation in joints for treatment of rheumatoid arthritis [110].

5.7. Antibody-conjugated nanoparticles

A new trend of targeted drug delivery systems is developing in nanomedicine. Numerous researchers are discovering new target-ing moieties and respective receptors to achieve successful formulations. The basic principle behind ligand-targeted thera-peutics is the association of molecules such as antibodies to the nanosystem. From this time, these ligands shall bind to target cells which receptors are either unique or excessively expressed, when comparing to normal tissue cells [111]. There are some examples of conjugation of NPs with antibodies, along with the outstanding properties of NPs such as their ability of working as drug carriers or intrinsic magnetic characteristics, with the targeting capacity [8]. A new type of anti-TNF-a antibody based on albumin was developed is camelid anti-TNF-a-anti-HSA trivalent nanobody is compounded of two

anti-TNF-a domains and one anti-HSA domain. This novel antibody (Ozralizumab) is under phase II clinical trial for treating RA [112,113]. Recombinant human IL- 1 receptor antagonist (rhIL-1ra), Anakinra, has been accepted for the treatment of patients with moderate-severe RA. Fusion protein composed of IL-1ra and HSA was developed which had signifi-cantly higher half-life compared to IL-1ra in plasma and selectively accumulated in the inflamed joints of a collagen-induced mouse RA model [114]. Recent approaches in nanotherapy used for drugs delivery in rheumatoid arthritis are summarized in Table 2.

6. Conclusion

Chronic inflammation plays a fundamental role in the development of many diseases such as rheumatoid arthritis. Consequently, the ability to treat such inflammation is critical in the prevention of associated afflictions. Drug therapies for the controlling of RA have made significant progress last decades. However, dose-limiting therapeutic indicator of current RA therapeutics impedes their optimal use and RA patients tolerate from severe negative side effects resultant from non-specific organ toxicity frequent and long-term treatment (Table 3). Nanosystems indicate specific and localized delivery of drugs while minimizing the quantity of drug used, so restrictive probable off-target unwanted effects. These systems can be let the prolonged use of NSAIDs and GCs in high-risk patient populations. Recently, there is remarkable attention in the development of inhibitors for the specific targeting of signaling pathways that drive inflammation [Janus kinase (JAK), spleen tyrosine kinase (Syk), and nuclear factor k-light-chainenhancer of activated B cells (NF-kB) pathways] [7]. But the oral uses of these agents lead to generalized suppression of multiple physiologic functions. So NP-based targeted drugs delivery systems is an ideal therapeutic approach to assess these signaling molecule inhibitors in the future. Finally, this review attentions on therapeutic attitudes for RA; however, there is always room for improvement, and further and more comprehen-sive studies should be conducted for nanomedicine therapeutic approaches to become a reality in the clinical practice of RA therapy.

References

[1] S. Mitragotri, J.-W. Yoo, Designing micro-and nano-particles for treating rheumatoid arthritis, Arch. Pharmacal Res. 34 (2011) 1887–1897.

[2] E. Schurgers, A. Billiau, P. Matthys, Collagen-induced arthritis as an animal model for rheumatoid arthritis: focus on interferon, J. Interferon Cytokine Res. 31 (2011) 917 926.

[3] M. Kourilovitch, C. Galarza-Maldonado, E. Ortiz-Prado, Diagnosis and classification of rheumatoid arthritis, J. Autoimmun. 48 (2014) 26–30.

[4] B. Yousefi, F. Jadidi-Niaragh, G. Azizi, F. Hajighasemi, A. Mirshafiey, The role of leukotrienes in immunopathogenesis of rheumatoid arthritis, Mod. Rheumatol. 24 (2014) 225–235.

[5] S. Viatte, D. Plant, S. Raychaudhuri, Genetics and epigenetics of rheumatoid arthritis, Nat. Rev. Rheumatol. 9 (2013) 141–153.

[6] C. Ospelt, S. Gay, Epigenetic Epidemiology of Inflammation and Rheumatoid Arthritis, Epigenetic Epidemiology: Springer, 2012, pp. 289–305.

[7] C.T. Pham, Nanotherapeutic approaches for the treatment of rheumatoid arthritis, Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol. 3 (2011) 607– 619.

[8] C. da Costa Moura, Development of Multifunctional Nanoparticles for Targeted Therapy and Imaging of Rheumatoid Arthritis: Faculty of Engineering, University of Porto, 2013.

[9] S.M. Paulissen, J.P. van Hamburg, W. Dankers, E. Lubberts, The role and modulation of CCR6+ Th17 cell populations in rheumatoid arthritis, Cytokine 74 (2015) 43–53.

[10] K. Roy, R.K. Kanwar, J.R. Kanwar, Molecular targets in arthritis and recent trends in nanotherapy, Int. J. Nanomed. 10 (2015) 5407.

[11] L. Danks, H. Takayanagi, Immunology and bone, J. Biochem.154 (2013) 29–39.

[12] Z. Szekanecz, A.E. Koch, Angiogenesis and its targeting in rheumatoid arthritis, Vascul. Pharmacol. 51 (2009) 1–7.

[13] Z. Szekanecz, T. Besenyei, A. Szentpetery, A.E. Koch, Angiogenesis and vasculogenesis in rheumatoid arthritis, Curr. Opin. Rheumatol. 22 (2010) 299–306.

[14] H.F. Zhou, H. Yan, A. Senpan, S.A. Wickline, D. Pan, G.M. Lanza, et al., Suppression of inflammation in a mouse model of rheumatoid arthritis using targeted lipase-labile fumagillin prodrug nanoparticles, Biomaterials 33 (2012) 8632–8640.

[15] W. Gao, C. Sweeney, C. Walsh, P. Rooney, J. McCormick, D.J. Veale, et al., Notch signalling pathways mediate synovial angiogenesis in response to vascular endothelial growth factor and angiopoietin 2, Ann. Rheum. Dis. 72 (2013) 1080–1088.

[16] Z. Jiao, W. Wang, J. Ma, S. Wang, Z. Su, H. Xu, Notch signaling mediates TNFa- induced IL-6 production in cultured fibroblast-like synoviocytes from rheumatoid arthritis, Clin. Dev. Immunol. 2012 (2011).

[17] W. Gao, C. Sweeney, M. Connolly, A. Kennedy, C.T. Ng, J. McCormick, et al., Notch-1 mediates hypoxia-induced angiogenesis in rheumatoid arthritis, Arthritis Rheumatism 64 (2012) 2104–2113.

[18] Y. Kochi, A. Suzuki, K. Yamamoto, Genetic basis of rheumatoid arthritis: a current review, Biochem. Biophys. Res. Commun. 452 (2014) 254–262.

[19] Y.K. Lee, S.K. Mazmanian, Has the microbiota played a critical role in the evolution of the adaptive immune system? Science 330 (2010) 1768–1773.

[20] K.P. Liao, L. Alfredsson, E.W. Karlson, Environmental influences on risk for rheumatoid arthritis, Curr. Opin. Rheumatol. 21 (2009) 279.

[21] K. Nishimura, D. Sugiyama, Y. Kogata, G. Tsuji, T. Nakazawa, S. Kawano, et al., Meta-analysis: diagnostic accuracy of anti–cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis, Ann. Intern. Med. 146 (2007) 797–808.

[22] N. Yukawa, T. Fujii, S. Kondo-Ishikawa, H. Yoshifuji, D. Kawabata, T. Nojima, et al., Correlation of antinuclear antibody and anti-double-stranded DNA antibody with clinical response to infliximab in patients with rheumatoid arthritis: a retrospective clinical study, Arthritis Res. Ther. 13 (2011) R213.
[23] P. Emery, I. McInnes, R. van Vollenhoven, M. Kraan, Clinical identification and treatment of a rapidly progressing disease state in patients with rheumatoid arthritis, Rheumatology 47 (2008) 392–398.
[24] E.W. St clair, D.M. van der Heijde, J.S. Smolen, R.N. Maini, J.M. Bathon, P. Emery, et al., Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial, Arthritis Rheumatism 50 (2004) 3432–3443.
[25] D.E. Trentham, A.S. Townes, A.H. Kang, Autoimmunity to type II collagen an experimental model of arthritis, J. Exp. Med. 146 (1977) 857–868.
[26] R.A. Bader, The Development of Targeted Drug Delivery Systems for Rheumatoid Arthritis Treatment, INTECH Open Access Publisher, 2012.
[27] P. Rao, E.E. Knaus, Evolution of nonsteroidal anti-inflammatory drugs (NSAIDs): cyclooxygenase (COX) inhibition and beyond, J. Pharm. Pharm. Sci. 11 (2008) 81–110.
[28] J.N. Hoes, J.W. Jacobs, F. Buttgereit, J.W. Bijlsma, Current view of glucocorticoid co-therapy with DMARDs in rheumatoid arthritis, Nat. Rev. Rheumatol. 6 (2010) 693–702.
[29] R. von Vollenohower, Treatment of rheumatoid arthritis: state of the art, Nat. Rev. Rheumatol. 5 (2009) 531–541.
[30] I.B. McInnes, J.R. O'Dell, State-of-the-art rheumatoid arthritis, Ann. Rheum. Dis. 69 (2010) 1898–1906.
[31] L. Šenolt, J. Vencovský, K. Pavelka, C. Ospelt, S. Gay, Prospective new biological therapies for rheumatoid arthritis, Autoimmun. Rev. 9 (2009) 102–107.
[32] F.M. Meier, M. Frerix, W. Hermann, U. Müller-Ladner, Current immunotherapy in rheumatoid arthritis, Immunotherapy 5 (2013) 955–974.
[33] C. Salliot, A. Finckh, W. Katchamart, Y. Lu, Y. Sun, C. Bombardier, et al., Indirect comparisons of the efficacy of biological antirheumatic agents in rheumatoid arthritis in patients with an inadequate response to conventional diseasemodifying antirheumatic drugs or to an anti-tumour necrosis factor agent: a meta-analysis, Ann. Rheum. Dis. 70 (2011) 266–271.
[34] C. Jorgensen, F. Apparailly, Prospects for gene therapy in inflammatory arthritis, Best Practice Res. Clin. Rheumatol. 24 (2010) 541–552.
[35] K.E. Lundin, O.E. Simonson, P.M. Moreno, E.M. Zaghloul, I.I. Oprea, M.G. Svahn, et al., Nanotechnology approaches for gene transfer, Genetica 137 (2009) 47– 56.
[36] S. Parveen, R. Misra, S.K. Sahoo, Nanoparticles: a boon to drug delivery, therapeutics, diagnostics and imaging, Nanomed. Nanotechnol. Biol. Med. 8 (2012) 147–166.
[37] R. Stevenson, A.J. Hueber, A. Hutton, I.B. McInnes, D. Graham, Nanoparticles and inflammation, Sci. World J. 11 (2011) 1300–1312.
[38] A.C. Anselmo, S. Mitragotri, Cell-mediated delivery of nanoparticles: taking advantage of circulatory cells to target nanoparticles, J. Control. Release 190 (2014) 531–541.
[39] E.C. Wang, A.Z. Wang, Nanoparticles and their applications in cell and molecular biology, Integr. Biol. 6 (2014) 9–26.
[40] A.M. Brynskikh, Y. Zhao, R.L. Mosley, S. Li, M.D. Boska, N.L. Klyachko, et al., Macrophage delivery of therapeutic nanozymes in a murine model of Parkinson's disease, Nanomedicine 5 (2010) 379–396.
[41] V.P. Torchilin, Recent advances with liposomes as pharmaceutical carriers, Nat. Rev. Drug Discov. 4 (2005) 145–160.
[42] P. Srinath, M. Chary, S. Vyas, P. Diwan, Long-circulating liposomes of indomethacin in arthritic rats—a biodisposition study, Pharm. Acta Helv. 74 (2000) 399–404.
[43] S. Palakurthi, S. Vyas, P. Diwan, Biodisposition of PEG-coated lipid microspheres of indomethacin in arthritic rats, Int. J. Pharm. 290 (2005) 55– 62.

[44] A. Bernardi, A. Zilberstein, E. Jäger, M. Campos, F. Morrone, J. Calixto, et al., Effects of indomethacin-loaded nanocapsules in experimental models of inflammation in rats, Br. J. Pharmacol. 158 (2009) 1104–1111.
[45] J.M. Metselaar, M.H. Wauben, J. Wagenaar-Hilbers, O.C. Boerman, G. Storm, Complete remission of experimental arthritis by joint targeting of glucocorticoids with long-circulating liposomes, Arthritis Rheumatism 48 (2003) 2059–2066.
[46] O.M.Y. Koo, I. Rubinstein, H. Önyüksel, Actively targeted low-dose camptothecin as a safe, long-acting, disease-modifying nanomedicine for rheumatoid arthritis, Pharm. Res. 28 (2011) 776–787.
[47] M. Khoury, P. Louis-Plence, V. Escriou, D. Noel, C. Largeau, C. Cantos, et al., Efficient new cationic liposome formulation for systemic delivery of small interfering RNA silencing tumor necrosis factor a in experimental arthritis, Arthritis Rheumatism 54 (2006) 1867–1877.
[48] V.P. Torchilin, Micellar nanocarriers: pharmaceutical perspectives, Pharm. Res. 24 (2007) 1–16.
[49] S.R. Grobmyer, N. Iwakuma, P. Sharma, B.M. Moudgil, What is Cancer Nanotechnology? Springer, 2010.
[50] S.H. Medina, M.E. El-Sayed, Dendrimers as carriers for delivery of chemotherapeutic agents, Chem. Rev. 109 (2009) 3141–3157.
[51] T. Ishihara, T. Kubota, T. Choi, M. Higaki, Treatment of experimental arthritis with stealth-type polymeric nanoparticles encapsulating betamethasone phosphate, J. Pharmacol. Exp. Ther. 329 (2009) 412–417.
[52] T. Ishihara, M. Takahashi, M. Higaki, Y. Mizushima, T. Mizushima, Preparation and characterization of a nanoparticulate formulation composed of PEG-PLA and PLA as anti-inflammatory agents, Int. J. Pharm. 385 (2010) 170–175.
[53] J. Hwang, K. Rodgers, J.C. Oliver, T. Schluep, a-Methylprednisolone conjugated cyclodextrin polymer-based nanoparticles for rheumatoid arthritis therapy, Int. J. Nanomed. 3 (2008) 359.
[54] N. Nagai, Y. Ito, Effect of solid nanoparticle of indomethacin on therapy for rheumatoid arthritis in adjuvant-Induced arthritis rat, Biol. Pharm. Bull. 37 (2014) 1109–1118.
[55] N. Nagai, C. Yoshioka, Y. Ito, Topical therapies for rheumatoid arthritis by gel ointments containing indomethacin nanoparticles in adjuvant-Induced arthritis rat, J. Oleo. Sci. 64 (2015) 337–346.
[56] E. Nogueira, A.C. Gomes, A. Preto, A. Cavaco-Paulo, Folate-targeted nanoparticles for rheumatoid arthritis therapy, Nanomed. Nanotechnol. Biol. Med. (2015).
[57] T.P. Thomas, S.N. Goonewardena, I.J. Majoros, A. Kotlyar, Z. Cao, P.R. Leroueil, et al., Folate-targeted nanoparticles show efficacy in the treatment of inflammatory arthritis, Arthritis Rheumatism 63 (2011) 2671–2680.
[58] B.B. Aggarwal, K.B. Harikumar, Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases, Int. J. Biochem. Cell Biol. 41 (2009) 40–59.
[59] A.K. Dewangan, S. Varkey, S., Mazumder Synthesis of Curcumin Loaded CMCAB Nanoparticles for Treatment of Rheumatoid Arthritis.
[60] R. Arora, A. Kuhad, I. Kaur, K. Chopra, Curcumin loaded solid lipid nanoparticles ameliorate adjuvant-induced arthritis in rats, Eur. J. Pain 19 (2015) 940–952.
[61] J. Ye, Q. Wang, X. Zhou, N. Zhang, Injectable actarit-loaded solid lipid nanoparticles as passive targeting therapeutic agents for rheumatoid arthritis, Int. J. Pharm. 352 (2008) 273–279.
[62] S.-M. Lee, H.J. Kim, Y.-J. Ha, Y.N. Park, S.-K. Lee, Y.-B. Park, et al., Targeted chemo-photothermal treatments of rheumatoid arthritis using gold halfshell multifunctional nanoparticles, ACS Nano 7 (2012) 50–57.
[63] R.I. Scheinman, R. Trivedi, S. Vermillion, U.B. Kompella, Functionalized STAT1 siRNA nanoparticles regress rheumatoid arthritis in a mouse model, Nanomedicine 6 (2011) 1669–1682.

[64] W.U. Kim, W.K. Lee, J.W. Ryoo, S.H. Kim, J. Kim, J. Youn, et al., Suppression of collagen-induced arthritis by single administration of poly (lactic-co-glycolic acid) nanoparticles entrapping type II collagen: a novel treatment strategy for induction of oral tolerance, Arthritis Rheumatism 46 (2002) 1109–1120.
[65] W.K. Lee, J.Y. Park, S. Jung, C.W. Yang, W.U. Kim, H.Y. Kim, et al., Preparation and characterization of biodegradable nanoparticles entrapping immunodominant peptide conjugated with PEG for oral tolerance induction, J. Control. Release 105 (2005) 77–88.
[66] H.A. Runnels, G.L. Weber, J. Min, E.M. Kudlacz, J.F. Zobel, C.B. Donovan, et al., PF-03475952: a potent and neutralizing fully human anti-CD44 antibody for therapeutic applications in inflammatory diseases, Adv. Ther. 27 (2010) 168– 180.
[67] J.-S. Park, S.-H. Kim, K. Kim, C.-H. Jin, K.Y. Choi, J. Jang, et al., Inhibition of Notch signalling ameliorates experimental inflammatory arthritis, Ann. Rheum. Dis. (2013), doi:http://dx.doi.org/10.1136/annrheumdis-2013- 203467.
[68] R. Heo, J.S. Park, H.J. Jang, S.-H. Kim, J.M. Shin, Y.D. Suh, et al., Hyaluronan nanoparticles bearing g-secretase inhibitor: in vivo therapeutic effects on rheumatoid arthritis, J. Control. Release 192 (2014) 295–300.
[69] H.F. Zhou, H.W. Chan, S.A. Wickline, G.M. Lanza, Pham CT. avb3-Targeted nanotherapy suppresses inflammatory arthritis in mice, FASEB J. 23 (2009) 2978–2985.
[70] A.C. Ma, T.K. Fung, R.H. Lin, M.I. Chung, D. Yang, S.C. Ekker, et al., Methionine aminopeptidase 2 is required for HSC initiation and proliferation, Blood 118 (2011) 5448–5457.
[71] H.F. Zhou, G. Hu, S.A. Wickline, G.M. Lanza, C.T. Pham, Synergistic effect of antiangiogenic nanotherapy combined with methotrexate in the treatment of experimental inflammatory arthritis, Nanomedicine 5 (2010) 1065–1074.
[72] T.A. Ahmed, B.M. Aljaeid, Preparation, characterization, and potential application of chitosan, chitosan derivatives, and chitosan metal nanoparticles in pharmaceutical drug delivery, Drug Design, Dev. Ther. 10 (2016) 483.
[73] Q. Yuan, S. Hein, R. Misra, New generation of chitosan-encapsulated ZnO quantum dots loaded with drug: synthesis: characterization and in vitro drug delivery response, Acta Biomater. 6 (2010) 2732–2739.
[74] S. Mansouri, Y. Cuie, F. Winnik, Q. Shi, P. Lavigne, M. Benderdour, et al., Characterization of folate-chitosan-DNA nanoparticles for gene therapy, Biomaterials 27 (2006) 2060–2065.
[75] M. Prabaharan, Chitosan-based nanoparticles for tumor-targeted drug delivery, Int. J. Biol. Macromol. 72 (2015) 1313–1322.
[76] M.J. Kim, J.-S. Park, S.J. Lee, J. Jang, J.S. Park, S.H. Back, et al., Notch1 targeting siRNA delivery nanoparticles for rheumatoid arthritis therapy, J. Control. Release 216 (2015) 140–148.
[77] S.J. Lee, A. Lee, S.R. Hwang, J.-S. Park, J. Jang, M.S. Huh, et al., TNF-a gene silencing using polymerized siRNA/thiolated glycol chitosan nanoparticles for rheumatoid arthritis, Mol. Ther. 22 (2014) 397–408.
[78] J.C. Fernandes, H. Wang, C. Jreyssaty, M. Benderdour, P. Lavigne, X. Qiu, et al., Bone-protective effects of nonviral gene therapy with Folate–Chitosan DNA nanoparticle containing Interleukin-1 receptor antagonist gene in rats with adjuvant-induced arthritis, Mol. Ther. 16 (2008) 1243–1251.
[79] G. Courties, M. Baron, J. Presumey, V. Escriou, P. van Lent, D. Scherman, et al., Cytosolic phospholipase A2a gene silencing in the myeloid lineage alters development of Th1 responses and reduces disease severity in collageninduced arthritis, Arthritis Rheumatism 63 (2011) 681–690.
[80] R.M. Samarasinghe, R.K. Kanwar, J.R. Kanwar, The effect of oral administration of iron saturated-bovine lactoferrin encapsulated chitosan-nanocarriers on osteoarthritis, Biomaterials 35 (2014) 7522–7534.
[81] F. Danhier, E. Ansorena, J.M. Silva, R. Coco, A. Le Breton, Préat V.PLGA-based nanoparticles: an overview of biomedical applications, J. Control. Release 161 (2012) 505–522.
[82] R. Weissleder, Molecular imaging in cancer, Science 312 (2006) 1168–1171.
[83] Y.-X.J. Wang, S.M. Hussain, G.P. Krestin, Superparamagnetic iron oxide contrast agents: physicochemical characteristics and applications in MR imaging, Eur. Radiol. 11 (2001) 2319–2331.

[84] M. Zhao, D.A. Beauregard, L. Loizou, B. Davletov, K.M. Brindle, Non-invasive detection of apoptosis using magnetic resonance imaging and a targeted contrast agent, Nat. Med. 7 (2001) 1241–1244.
[85] J. Ringe, M. Sittinger, Tissue engineering in the rheumatic diseases, Arthritis Res. Ther. 11 (2009) 211.
[86] C. Bouffi, F. Djouad, M. Mathieu, D. Noël, C. Jorgensen, Multipotent mesenchymal stromal cells and rheumatoid arthritis: risk or benefit, Rheumatology 48 (2009) 1185–1189.
[87] Y. Chen, J.-Z. Shao, L.-X. Xiang, X.-J. Dong, G.-R. Zhang, Mesenchymal stem cells: a promising candidate in regenerative medicine, Int. J. Biochem. Cell Biol. 40 (2008) 815–820.
[88] B.J. Jones, S.J. McTaggart, Immunosuppression by mesenchymal stromal cells: from culture to clinic, Exp. Hematol. 36 (2008) 733–741.
[89] H. Markides, O. Kehoe, R.H. Morris, A.J. El Haj, Whole body tracking of superparamagnetic iron oxide nanoparticle-labelled cells—a rheumatoid arthritis mouse model, Stem Cell Res. Ther. 4 (2013) 126.
[90] K.J. Saldanha, R.P. Doan, K.M. Ainslie, T.A. Desai, S. Majumdar, Micrometer- sized iron oxide particle labeling of mesenchymal stem cells for magnetic resonance imaging-based monitoring of cartilage tissue engineering, Magn. Reson. Imaging 29 (2011) 40–49.
[91] G. He, H. Zhang, H. Wei, Y. Wang, X. Zhang, Y. Tang, et al., In vivo imaging of bone marrow mesenchymal stem cells transplanted into myocardium using magnetic resonance imaging: a novel method to trace the transplanted cells, Int. J. Cardiol. 114 (2007) 4–10.
[92] T.H. Kim, J.K. Kim, W. Shim, S.Y. Kim, T.J. Park, J.Y. Jung, Tracking of transplanted mesenchymal stem cells labeled with fluorescent magnetic nanoparticle in liver cirrhosis rat model with 3-T MRI, Magn. Reson. Imaging 28 (2010) 1004–1013.
[93] H.S. Kim, S.Y. Oh, H.J. Joo, K.R. Son, I.C. Song, W.K. Moon, The effects of clinically used MRI contrast agents on the biological properties of human mesenchymal stem cells, NMR Biomed. 23 (2010) 514–522.
[94] J. Duan, J. Dong, T. Zhang, Z. Su, J. Ding, Y. Zhang, et al., Polyethyleneimine- functionalized iron oxide nanoparticles for systemic siRNA delivery in experimental arthritis, Nanomedicine 9 (2014) 789–801.
[95] X. Huang, Jain PK, El-Sayed IH, El-Sayed MA. Gold nanoparticles: interesting optical properties and recent applications in cancer diagnostics and therapy. (2007).
[96] G. Peng, U. Tisch, O. Adams, M. Hakim, N. Shehada, Y.Y. Broza, et al., Diagnosing lung cancer in exhaled breath using gold nanoparticles, Nat. Nanotechnol. 4 (2009) 669–673.
[97] X. Liu, Q. Dai, L. Austin, J. Coutts, G. Knowles, J. Zou, et al., A one-step homogeneous immunoassay for cancer biomarker detection using gold nanoparticle probes coupled with dynamic light scattering, J. Amer. Chem. Soc. 130 (2008) 2780–2782.
[98] X. Huang, I.H. El-Sayed, W. Qian, M.A. El-Sayed, Cancer cell imaging and photothermal therapy in the near-infrared region by using gold nanorods, J. Amer. Chem. Soc. 128 (2006) 2115–2120.
[99] P. Mukherjee, R. Bhattacharya, P. Wang, L. Wang, S. Basu, J.A. Nagy, et al., Antiangiogenic properties of gold nanoparticles, Clin. Cancer Res. 11 (2005) 3530–3534.
[100] C. Brown, M. Whitehouse, E.R.T. Tiekink, G.R. Bushell, Colloidal metallic gold is not bio-inert, Inflammopharmacology 16 (2008) 133–137.
[101] J.S. Ma, W.J. Kim, J.J. Kim, T.J. Kim, S.K. Ye, M.D. Song, et al., Gold nanoparticles attenuate LPS-induced NO. production through the inhibition of NF-kB and IFN-b/STAT1 pathways in RAW264. 7 cells, Nitric Oxide 23 (2010) 214–219.
[102] L.R. James, Z.-Q. Xu, R. Sluyter, E.L. Hawksworth, C. Kelso, B. Lai, et al., An investigation into the interactions of gold nanoparticles and anti-arthritic drugs with macrophages, and their reactivity towards thioredoxin reductase, J. Inorg. Biochem. 142 (2015) 28–38.
[103] H. Lee, M.-Y. Lee, S.H. Bhang, B.-S. Kim, Y.S. Kim, J.H. Ju, et al., Hyaluronate— Gold Nanoparticle/Tocilizumab complex for the treatment of rheumatoid arthritis, ACS Nano 8 (2014) 4790–4798.

[104] B. Elsadek, F. Kratz, Impact of albumin on drug delivery—New applications on the horizon, J. Control. Release 157 (2012) 4–28.
[105] W.J. Gradishar, S. Tjulandin, N. Davidson, H. Shaw, N. Desai, P. Bhar, et al., Phase III. trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer, J. Clin. Oncol. 23 (2005) 7794–7803.
[106] M.J. Hawkins, P. Soon-Shiong, N. Desai, Protein nanoparticles as drug carriers in clinical medicine, Adv. Drug Deliv. Rev. 60 (2008) 876–885.
[107] E. Neumann, E. Frei, D. Funk, M.D. Becker, H.-H. Schrenk, U. Müller-Ladner, et al., Native albumin for targeted drug delivery, Expert Opin. Drug Deliv. 7 (2010) 915–925.
[108] C. Fiehn, E. Neumann, A. Wunder, S. Krienke, S. Gay, U. Müller-Ladner, Methotrexate (MTX) and albumin coupled with MTX (MTX-HSA) suppress synovial fibroblast invasion and cartilage degradation in vivo, Ann. Rheum. Dis. 63 (2004) 884–886.
[109] P. Patel, H. Patel, S. Panchal, T. Mehta, Formulation strategies for drug delivery of tacrolimus: an overview, Int. J. Pharm. Invest. 2 (2012) 169.
[110] H.J. Byeon, C. Lee, S. Lee, E.S. Lee, H.-G. Choi, E.-S. Park, et al., Pharmaceutical potential of tacrolimus-loaded albumin nanoparticles having targetability to rheumatoid arthritis tissues, Int. J. Pharm. 497 (2016) 268–276.
[111] E. Blanco, A. Hsiao, A.P. Mann, M.G. Landry, F. Meric-Bernstam, M. Ferrari, Nanomedicine in cancer therapy: innovative trends and prospects, Cancer Sci. 102 (2011) 1247–1252.
[112] K. Coppieters, T. Dreier, K. Silence, H.D. Haard, M. Lauwereys, P. Casteels, et al., Formatted anti?tumor necrosis factor a VHH proteins derived from camelids show superior potency and targeting to inflamed joints in a murine model of collagen-induced arthritis, Arthritis Rheumatism 54 (2006) 1856–1866.
[113] K. Ren, A. Dusad, R. Dong, L. Quan, Albumin as a delivery carrier for rheumatoid arthritis, J. Nanomed. Nanotechol. 4 (2013) 2.
[114] M. Liu, Y. Huang, L. Hu, G. Liu, X. Hu, D. Liu, et al., Selective delivery of interleukine-1 receptor antagonist to inflamed joint by albumin fusion, BMC Biotechnol. 12 (2012) 68.